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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	14

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No	Applicant(s)
09/368,670	Llinas-Brunet
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on Jun 21, 2001

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) X Claim(s) 1-28, 30-35, 37-92, and 96-102 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from consider

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) 1-28, 30-35, 37-92, and 96-102 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of

1 ☐ Certified copies of the priority documents have been received.

2 ☐ Certified copies of the priority documents have been received in Application No.

3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other: _____

Pursuant to the directives of paper No. 12 (filed 6/4/01), claims 1, 40, 45, 47-49, 59, 60, 72-74, 76 have been amended. Claims 1-28, 30-35, 37-92, 96-102 remain pending. While the previously imposed restriction is not "withdrawn", the elected group is now extended to encompass all compounds that are currently encompassed by claim 1, as well as methods of making and using those compounds.

Claims 1-28, 30-35, 37-92, 96-102 are examined in this Office action.

Applicants' arguments filed 6/4/01 have been considered and found persuasive in part. Claims which had recited the terms "pharmaceutical" or "pharmaceutically" were rejected. Those claims in which the "offending" term has been deleted (and replaced with the term "non-toxic") are no longer rejected.

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This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 with regard to the sequence disclosures.

A sequence listing has been submitted, but contains errors, as indicated on the accompanying sheets.

Applicant is given the time period set in this letter within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result

in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 96-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention.

The cited claims recite one or more of the following terms: "pharmaceutical", "pharmaceutically", and/or "therapeutically". As indicated previously, the first two of these imply therapeutic efficacy, and the third, of course, explicitly recites it. Applicants have shown that several of the claimed compounds are effective to inhibit HCV protease *in vitro*. However, treatment of the disease is another matter altogether. It is suggested that applicants claim one or more of the following:

> *200. A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) comprising contacting HCV NS3 protease with a compound of claim 1 for a time and under conditions effective to inhibit HCV NS3 protease.*

201. A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) in a cell comprising contacting a cell containing HCV NS3 protease with a compound of claim 1 for a time and under conditions effective to inhibit HCV NS3 protease.

202. A method of inhibiting hepatitis C nonstructural protein-3 protease (HCV NS3 protease) in a human infected with hepatitis C virus comprising administering a compound of claim 1 to said human for a time and under conditions effective to inhibit HCV NS3 protease.

203. A method of inhibiting replication of hepatitis C virus comprising contacting hepatitis C virus with a compound of claim 1 for a time and under conditions effective to inhibit HCV NS3 protease.

204. A method of inhibiting replication of hepatitis C virus in a mammal infected with hepatitis C virus comprising administering a compound of claim 1 to said mammal for a time and under conditions effective to inhibit HCV NS3 protease.

Notwithstanding the foregoing, "treatment" of hepatitis C infections in mammals is another matter altogether. It is not established that the NS3 protease will be inhibited to an extent which is sufficient to actually cause a reduction in viral titers. For example, if the virus is replicating at a rate of 100 "units" per day in the absence of the compound, and 90 units per day in the presence of the compound, one could say that inhibition had been achieved. However, if the virus is replicating at a rate of 90 per day in spite of the presence of the compound (of claim 1), the patient's condition will still worsen, and "treatment" will not have been achieved.

In addition to the foregoing, the claims encompass processes in which neither the time, nor the conditions are effective to inhibit the HCV NS3 protease. This ground of rejection can

be overcome by reciting that the time and conditions are indeed effective to achieve this objective.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As it happens, structure/activity relationships are unpredictable. As observed by Tung (WO 98/17679), compounds within that disclosed genus (table 9, pp. 106-107) exhibited more than a 100-fold range of efficacies in the inhibition of HCV NS3 protease. Many of those compounds characterized as exhibiting an inhibition above 100 *micro*molar may have been completely inactive. (See also table I of WO 99/07734). Thus, one question is, can applicants look at a structure and determine its activity, even *in vitro*? And if not, how can applicants make predictions about what will happen *in vivo*? As for the "state of the art", there is no evidence that anyone has effectively treated an HCV infection in a mammal using an inhibitor of HCV NS3 protease. Moreover, as stated in Ingallinella (*Biochem* **37**, 8906, 1998) at page 8906, col 1:

"Neither an effective therapy for HVC nor a vaccine... has ... been developed".

In accordance with the foregoing, "undue experimentation" would be required to practice the claimed invention.

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Claims 1-28, 30-35, 37-92, 96-102 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 9-11 make reference to the side chains of certain D- or L- amino acids. However, the side chain of e.g., D-aspartic acid is entirely indistinguishable from the the side chain of L-aspartic acid. Accordingly, if side chains are going to be recited, the stereochemistry becomes entirely superfluous.

- In claim 26, the very last character present at the end of the last line of text on page 153 is a hyphen. If the hyphen is going to be present, it must be adjacent to something.

- In claim 30, the penultimate Markush Group member should be preceded by the conjunction "and".

- Claim 45 is rendered indefinite by recitation of the terms "racemic mixture of diasteriomers" and "racemic mixture of optical isomers". In principle, applicants could claim any of the following:

45. A compound of fomrula Ib or a diasteriomer or an optical isomer thereof...etc.

103. A mixture consisting of a compound according to claim 45, and at least one stereoisomer thereof.

104. The mixture according to claim 103 which consists of several diasteriomers of a compound according to claim 45.

105. The mixture according to claim 104, wherein at least two of said diasteriomers are racemates of one another.

106. The mixture according to claim 103, consisting of 100 stereoisomers of a compound according to claim 45, each of which is a racemate of another compound

present in the mixture.

107. The mixture according to claim 106, wherein 50 pairs of racemates are present.
108. The mixture according to claim 107, wherein the molar ratio of each member of the pair is 1:1.

- In claim 75, the abbreviation "acca" appears. If this term is going to be used, it must be defined somewhere in the claim.

- In claim 78, the designation "Tab.7" occurs. Here, the period between "Tab" and "7" should be eliminated.

- In claim 86, the penultimate Markush Group member should be preceded by the conjunction "and".

- Claim 89, line 1 makes reference to a "peptide analog". However, this term does not appear in claim 1.

- In claim 89, the term "APG" is used. If this term is going to be used, it must be defined somewhere in the claim.

- In claim 89, it is not entirely clear what P2, P3...P6 refer to. One of the issues here is that of protecting groups. Are the amino acids protected, and if so, at what point are the protecting groups removed?

- Claim 89 is indefinite because it omits process steps. Apart from the issue of protection/deprotection, there is the matter of isolation of the final product. If the final product is never isolated, how can it ever be used? It is suggested that the claim be amended to recite a step for isolation of the final product. There is also another issue. The claim recites, for one embodiment, that by coupling APG-P2 with the aminocyclopropyl compound, the compound of formula I can be synthesized. However, there are no compounds within the scope of claim 1 that can be synthesized according to this coupling step alone. The same is true of APG-P3-P2. Even for the case of APG-P4-P3-P2, there is ambiguity. Claim 1 does permit integer variables "a" and "b" to be zero, but does not require it. The same issues apply in the case of claims 90-91.

- In claim 98, the abbreviation "NS3" may be used, but only if accompanied by the full name.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton. Phone: (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600